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Fragmentation of the rest-activity rhythm correlates with age-related cognitive deficits

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SUMMARY Aging affects both cognitive performance and the sleep-wake rhythm. The recent surge of studies that support a role of sleep for cognitive performance in healthy young adults suggests that disturbed sleep-wake rhythms may contribute to ‘age-related’ cognitive decline. This relationship has however not previously been extensively investigated. The present correlational study integrated a battery of standardized cognitive tests to investigate the association of mental speed, memory, and executive function with actigraphically recorded sleep-wake rhythms in 144 home-dwelling elderly participants aged 69.5 ± 8.5 (mean \pm SD). Multiple regression analyses showed that the partial correlations of the fragmentation of the sleep-wake rhythm with each of the three cognitive domains ($r = -0.16$, -0.19 , and -0.16 respectively) were significant. These associations were independent from main effects of age, implying that a unique relationship between the rest-activity rhythm and cognitive performance is present in elderly people.

KEYWORDS actigraphy, aging, circadian rhythm, cognitive function, sleep

INTRODUCTION

Alterations in circadian rhythms in physiology and behavior are commonly observed in elderly people and include sleep-wake rhythm disturbances such as nocturnal activity, sleep fragmentation, daytime naps and a reduction of circadian amplitude (Bliwise *et al.*, 2005; Huang *et al.*, 2002). Previous work in young adults supports a relationship between decreased sleep quality and a decline in cognitive functions. Several studies have explored and confirmed an association between cognitive functions and sleep disorders such as obstructive sleep apnea (Aloia *et al.*, 2003) or chronic insomnia (Bastien *et al.*, 2003). However, only limited attention has been paid to the possible contribution of the frequently disturbed

sleep-wake rhythms to what has been regarded a *normal age-related decline* in cognitive performance. A previous report on a large study that included actigraphic sleep estimates confirms that disturbed sleep increases the risk of present and future below-cut-off ratings on the Mini-Mental State Examination (MMSE) and Trail Making Test (Blackwell *et al.*, 2006).

Extending on these previous studies, we here investigated whether not only nocturnal sleep, but also the circadian organization of the sleep-wake *rhythm* has predictive value for cognitive functioning in home-dwelling elderly people. Marked changes in the sleep-wake rhythm with aging have been shown in both human and non-human primates (Cayetanot *et al.*, 2005; Huang *et al.*, 2002). Previous studies in adult animals and humans have shown that cognitive performance is not only sensitive to disruptions within the period of sleep, but also to disruptions of such regularity in the 24-h pattern in sleep and wakefulness (e.g. Cho, 2001; Fekete *et al.*, 1985; Van Someren and Riemersma - Van Der Lek, 2007 for a review). In demented

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elderly, Carvalho-Bos *et al.* (2007) demonstrated that the day-to-day stability of the sleep-wake rhythm profile was a better predictor of cognitive disturbances than e.g. nocturnal restlessness *per se*. Concertedly, these findings make it likely that age-related changes in the sleep-wake rhythm could be associated with age-related changes in cognitive performance.

It was our primary aim to investigate this relationship. Sleep-wake rhythm disturbances were quantified using actigraphy according to previously described and validated non-parametric methods yielding variables that quantify the amplitude, regularity and fragmentation of the sleep-wake rhythm (Carvalho-Bos *et al.*, 2007; Van Someren, 2007). Cognitive functions strongly affected by aging are mental speed, memory, and executive function (e.g. Bopp and Verhaeghen, 2005; van Hooren *et al.*, 2007; MacPherson *et al.*, 2002). We evaluated whether these cognitive domains were similarly related to disturbed sleep-wake rhythms. To obtain reliable estimates, each of these cognitive domains was assessed using multiple standardized neuropsychological tests.

METHODS

Study population

A detailed description of the 162 participants is available in a published report (Oosterman *et al.*, 2008). Of these, a complete dataset (see results) was available for 144 people, 90 males and 54 females, aged 69.5 ± 8.5 years (mean \pm SD), range 50–91. As this study was part of a larger study on the effects of cardiovascular risk factors, most participants included were diagnosed with one or more of these risk factors. In brief, participants were recruited among people visiting the outpatient clinic (of cardiology, internal medicine, or neurology) of the Sint Lucas Andreas Hospital in Amsterdam, the Netherlands. Most participants (82.7%) scored positive for at least one of the cardiovascular risk factors, including cardiac disease, diabetes mellitus, hypertension, smoking, and hypercholesterolemia. A minority ($n = 11$) of the participants were either spouses or friends of the recruited visitors of the outpatient clinics. Participants with a history of neurodegenerative disease (e.g. dementia, Parkinson's disease), stroke, pacemaker implant, psychiatric illness, and alcohol or other substance abuse, and an MMSE (Folstein *et al.*, 1975) score < 24 were excluded. The use of hypnotic medication (e.g. benzodiazepine) was evaluated from a patient interview and the medical records. IQ was assessed with the Dutch version of the National Adult Reading Test (Schmand *et al.*, 1991). Approval for the study was obtained from the local medical ethics committee. All participants signed an informed consent.

Rest-activity rhythm

The rest-activity rhythm was assessed for 7 days continuously using actigraphy, the recording of wrist accelerations (Actiwatch, Cambridge Neurotechnology, Cambridge, UK). The

activity profile was quantified with three previously described variables reflecting different aspects of the variability in the hour-by-hour activity (Carvalho-Bos *et al.*, 2007). The inter-daily stability (IS) quantifies the extent to which all recorded 24-h activity profiles resemble each other, i.e. the day-by-day regularity of the sleep-wake pattern. The intradaily variability (IV) quantifies the fragmentation of the rhythm, i.e. the frequency and extent of transitions between periods of rest and activity. Finally, a non-parametric measure of the amplitude of the rhythm (AMP) was calculated by subtracting the average activity during the least active 5-h period (L5) of the average 24-h profile from the average activity during the most active 10-h period (M10).

Cognitive functions

Mental speed, memory, and executive function were evaluated using a concise neuropsychological test battery as described below.

Mental speed

Stroop test (Stroop, 1935). The Word (W) and Color (C) cards of the Stroop test were assessed as a first measure to operationalize processing speed. For the C/W card, see the Executive function section below. The W card consists of 10 rows with 10 color names each of which are printed in black ink. The participant is required to read aloud these color names as fast as possible. For the C card, 10 rows, with each row containing 10 colored blocks, are presented, which the participant is required to name as fast as possible. The time needed to finish the cards was measured.

Trail Making Test (Reitan, 1958). Part A of the Trail Making Test was assessed as a second measure to operationalize processing speed. For part B, see the Executive function section below. In part A, a sheet of paper is presented on which 25 encircled numbers are randomly distributed. The participant is required to sequentially connect these numbers as fast as possible. Completion time was measured.

Memory

15-words test. The Dutch version (Saan and Deelman, 1986) of the Auditory Verbal Learning Test (Rey, 1964) was used to measure verbal memory. A list of 15 unrelated words is presented five times. After each presentation, the participant is requested to repeat as many words as possible. The total number of words retained was taken as a first measure for memory performance.

Digit span forward (Wechsler, 1987). In the Digit span test, an order of digits is presented orally. Following presentation, participants are requested to repeat the digits in the same order. For each number of digits, two sequences were presented and set size increased with one digit in case at least

one sequence was successfully reproduced. The total number of correct reproductions was taken as a second measure of memory performance.

Pattern recognition memory (CANTAB). This visual recognition memory test included in the CANTAB consists of two series of 12 visual patterns each. For each series the patterns are presented serially, after which the participant is presented with 12 pairs of two patterns each, of which the one that had previously been presented has to be identified. The number of correct responses (maximum of 24) was taken as a third measure for memory performance.

Executive function

Digit span backward (Wechsler, 1987). Similar to the forward version discussed above, an order of digits is presented orally, only this time participants are requested to repeat the digits in the reversed order (backward version). The total number of correct reversed reproductions was taken as an index of working memory performance.

Stroop test (Stroop, 1935). On the third, Color/Word (C/W) card of the Stroop task introduced above, color names are printed in an incongruent color, and the participant is required to name the colors in which the words are printed. The time needed to finish the card was measured. The so called interference time was calculated by subtracting the time needed to finish the C card (See Mental speed section) from the time needed to finish the C/W card. The interference time was regarded as a second measure of executive function.

Trail Making Test (Reitan, 1958). In part B of the Trail Making Test, both numbers and letters are distributed. The participant is instructed to serially and alternately draw connecting lines between the numbers and letters (i.e. 1, A, 2, B, 3, etc.). The completion time of part B divided by the completion time for part A (see also Mental speed section), assessing flexibility performance, was calculated as a third measure of executive function.

Statistical analysis

All analyses were performed using SPSS version 14.0 (SPSS, Inc., Chicago, IL, USA). The raw values on each subtest were *z*-transformed and subsequently average *z*-values were calculated within each cognitive domain, resulting in (i) a mental speed rating derived from the Stroop W, Stroop C and Trail Making Test A tests; (ii) a memory rating derived from the 15-word list, Digit span forward and Pattern recognition memory tests; and (iii) an executive function rating derived from the Digit span backward, Stroop C/W–Stroop C and Trail Making Test B/A. *z*-transformed subtest scores were multiplied by -1 as required such that a higher score always represented better performance.

Pearson correlations were calculated between each of the cognitive domain summary ratings and the rest-activity variables. To assure that significant associations were not restricted to the calculated summary ratings, correlations between single test scores and the rest-activity rhythm variables are also presented.

Secondly, independent regression coefficients of each possible predictor (rest-activity rhythm variables and confounders) were calculated for each cognitive domain separately. Confounders considered included age, gender, IQ, hypnotic medication, diabetes mellitus, hypertension, cardiac disease, hypercholesterolemia, and smoking. To determine the aspects of the rest-activity rhythm and the possible confounders that were most relevant to cognitive functioning, we performed multiple regression analyses with stepwise selection. The significance threshold for entry in the regression model was set at $P < 0.05$.

RESULTS

Of the 162 participants initially enrolled into the study, 16 participants were not included in the analysis because of failing or incomplete actigraphic recordings. Additionally, IQ estimates were unavailable for two participants. A complete dataset was available for 144 participants. These were 90 males and 54 females, aged 69.5 ± 8.5 years (mean \pm SD) with an IQ of 98.9 ± 13.4 and an MMSE of 27.9 ± 1.6 .

As shown in Table 1, highly significant correlations were present between the three cognitive summary ratings and the fragmentation and amplitude of the rest-activity variables. Similar significant correlations were observed between the individual subtest scores and IV and AMP. As the stability of the rest-activity rhythm (IS) was unrelated to the cognitive summary ratings, this variable was not further examined. Next to the two correlated rest-activity variables, several confounders, such as age, were strongly related to the cognitive summary ratings (Table 2). Stepwise regression analysis revealed that fragmentation of the rhythm (IV) significantly predicted all three cognitive summary ratings (mental speed: $\beta = -0.16$, $P < 0.05$; memory: $\beta = -0.19$, $P < 0.01$; executive function: $\beta = -0.16$, $P < 0.05$), despite that the predictive value of IV for each of the three cognitive summary ratings was decreased following inclusion of possible confounders (Table 2). No additional variation in the cognitive summary ratings was accounted for by AMP.

To determine the uniqueness of the association between IV and each cognitive domain, partial correlations were calculated between IV and each cognitive domain, while controlling for the other cognitive domains. Significant correlations were revealed between IV and mental speed ($r = -0.19$, $P < 0.05$) and executive function ($r = -0.17$, $P < 0.05$). Memory, however, was no longer significantly related to IV after controlling for mental speed and executive function ($r = -0.05$, $P = 0.59$), suggesting that the correlation between IV and memory function is mainly because of

Table 1 Correlations between cognitive functions and the rest-activity rhythm

| Cognitive function | Rest-activity rhythm | | |
|----------------------------|----------------------|----------|---------|
| | IS | IV | AMP |
| Mental speed | 0.07 | -0.35*** | 0.22** |
| TMTA | 0.11 | -0.36*** | 0.19* |
| Stroop W | 0.04 | -0.30*** | 0.21* |
| Stroop C | 0.05 | -0.21* | 0.15 |
| Memory | -0.02 | -0.31*** | 0.20* |
| 15-word list | -0.01 | -0.34*** | 0.22** |
| Digit span forward | 0.00 | -0.15 | 0.17* |
| Pattern recognition memory | -0.06 | -0.20* | 0.05 |
| Executive function | 0.07 | -0.36*** | 0.27*** |
| TMTB/TMTA | -0.01 | -0.23** | 0.16 |
| Stroop C/W–Stroop C | 0.10 | -0.36*** | 0.27*** |
| Digit span backward | 0.03 | -0.20* | 0.16 |

Correlations between cognitive functions (domains and the separate tests that comprise that domain) and rest-activity variables are displayed. Higher cognitive scores always reflect better performance. AMP, amplitude; IS, interdaily stability; IV, intradaily variability; Stroop C, stroop color; Stroop W, stroop word; Stroop C/W, stroop color/word; TMTA, Trail Making Test part A; TMTB, Trail Making Test part B.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

the involvement of mental speed and executive function in the memory tasks.

Figure 1 gives a graphical representation of the relationship between IV and cognition. Participants were grouped in four quartiles according to their IV value, and average cognitive summary ratings were calculated for each quartile. Figure 2 illustrates the rest-activity rhythm of a participant with low IV and above average level of cognitive function and the rest-activity rhythm of a participant with high IV and below average level of cognitive function respectively.

DISCUSSION

The present study revealed that the rest-activity rhythm variable that is most strongly associated with aging, i.e. the fragmentation (IV, Huang *et al.*, 2002), predicts all cognitive functions examined, i.e. mental speed, memory, and executive function. Partial correlations showed that the association of rhythm fragmentation with cognitive decline is partly independent from main effects of age. This suggests that a part of what is called 'age-related' cognitive decline could independently be associated with the rest-activity rhythm. Our findings extend previous observations of a relationship between cognitive functions and either objective (e.g. Blackwell *et al.*, 2006) or subjective (e.g. Jellic *et al.*, 2002) measures of sleep quality. We here demonstrate that not only sleep but also its circadian organization is significantly related to cognitive decline. Of the three cognitive domains most affected by aging, mental speed was most strongly related to fragmentation of the sleep-wake rhythm; as compared with the participants with an IV in the first quartile, those in the second quartile already show a much worse performance on mental speed tests (see Fig. 1). The primary sensitivity of mental speed is in accordance with previous studies suggesting that much of the age-related cognitive decline is caused by a reduction in speed (e.g. Salthouse *et al.*, 1996). More specifically, tests of processing speed may be most sensitive to detect even minor age-related decline.

The present study significantly contributes to our current knowledge regarding possible associates of age-related cognitive decline. Next to age, factors known to induce cognitive decline in aging include, for example, cardiovascular risk factors (Halling and Berglund, 2006; Xiong *et al.*, 2006), depression (Sachs-Ericsson *et al.*, 2005) and presence of apolipoprotein E4 (Packard *et al.*, 2007). We here identified the fragmentation of the rest-activity rhythm as an additional

Table 2 Predictors of cognitive performance

| | β | | | | | |
|--------------|--------------|---------------------------|----------|---------------------|--------------------|---------------------------------|
| | Mental speed | Mental speed [†] | Memory | Memory [†] | Executive function | Executive function [†] |
| Age | -0.43*** | -0.32*** | -0.34*** | -0.20*** | -0.43*** | -0.32* |
| Gender | -0.06 | – | -0.02 | – | -0.07 | – |
| Hypnotics | -0.03 | – | -0.07 | – | 0.04 | – |
| IQ | 0.45*** | 0.37*** | 0.52*** | 0.46*** | 0.51*** | 0.43*** |
| DM | -0.01 | – | -0.19* | – | -0.12 | – |
| Hypertension | -0.09 | – | -0.11 | – | -0.12 | – |
| Hyperchol. | -0.17* | – | -0.16* | – | -0.07 | – |
| CVD | -0.27** | – | -0.18* | – | -0.19* | – |
| Smoking | -0.16 | -0.15* | -0.11 | – | -0.16* | -0.16* |
| IV | -0.35*** | -0.16* | -0.31** | -0.19** | -0.36*** | -0.16* |
| AMP | 0.22** | – | 0.20* | – | 0.27** | – |

In the first row simple standardized regression coefficients are presented for each individual predictor. In the second analysis, denoted with a [†], regression analyses with a stepwise selection procedure were performed to allow only significant predictors in the model. With regard to the cognitive performance measures, scores were adjusted such that a higher score always represents better performance.

AMP, amplitude; DM, diabetes mellitus; Hyperchol., hypercholesterolemia; IV, intradaily variability.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

strong factor involved. Although based on correlations, it is tempting to suggest that the fragmentation of the sleep-wake rhythm aggravates age-related cognitive decline. This is supported by studies showing a decrease in cognitive functions following sleep deprivation (Killgore *et al.*, 2006; Nilsson *et al.*, 2005), suggesting that a disrupted sleep-wake cycle

predicts cognitive dysfunction. Presumably, sleep deprivation reduces neural activity and thereby cognitive performance (e.g. Mu *et al.*, 2005). These effects may be even more pronounced with increasing age (Killgore *et al.*, 2006) and may explain the relationship between the rest-activity rhythm and cognition in the current study. The fact that the association of rhythm fragmentation with cognitive decline is partly independent of the association of age with cognitive decline warrants further experimental research into this relationship. Because the experimental or profession-related enforcement of irregular sleep-wake rhythms on rats or humans affects cognitive performance (Cho, 2001; Fekete *et al.*, 1985; Tapp and Holloway, 1981), an intriguing possibility to be evaluated in future research is whether the enforcement of a clear 24-h rhythm can attenuate in part the typical age-related cognitive decline.

Nonetheless, the direction of this relationship remains an issue of debate; although it is possible that an increase in fragmentation of the rest-activity rhythm exaggerates age-related cognitive decline, the opposite is also possible. High volitional lifestyle, which is characterized by more mental activity during the daytime, predicts better sleep quality in elderly people (Shirota *et al.*, 2001). This implies that better cognitive task performance may be a predictor of less fragmentation of the rest-activity rhythm in the current study. However, studies in which the level of cognitive activity was experimentally manipulated are inconclusive. For example, De Bruin *et al.* (2002) did not observe a relationship between the level of mental activity and sleep intensity, although heavy mental activity was related to less wakefulness shortly after

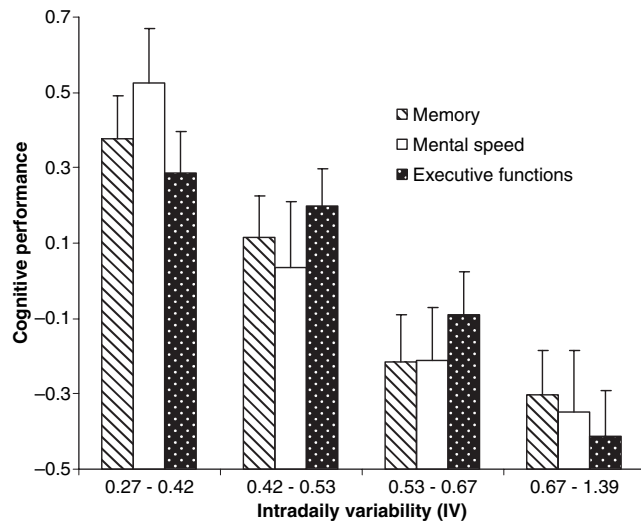


Figure 1. Cognitive performance in relation to fragmentation of the rest-activity rhythm. Four equal groups were created according to increasing rest-activity fragmentation scores (IV, 0.27–0.42, 0.42–0.53, 0.53–0.67, 0.67–1.39). Cognitive performance reflects average z-score (\pm SEM) for each domain.

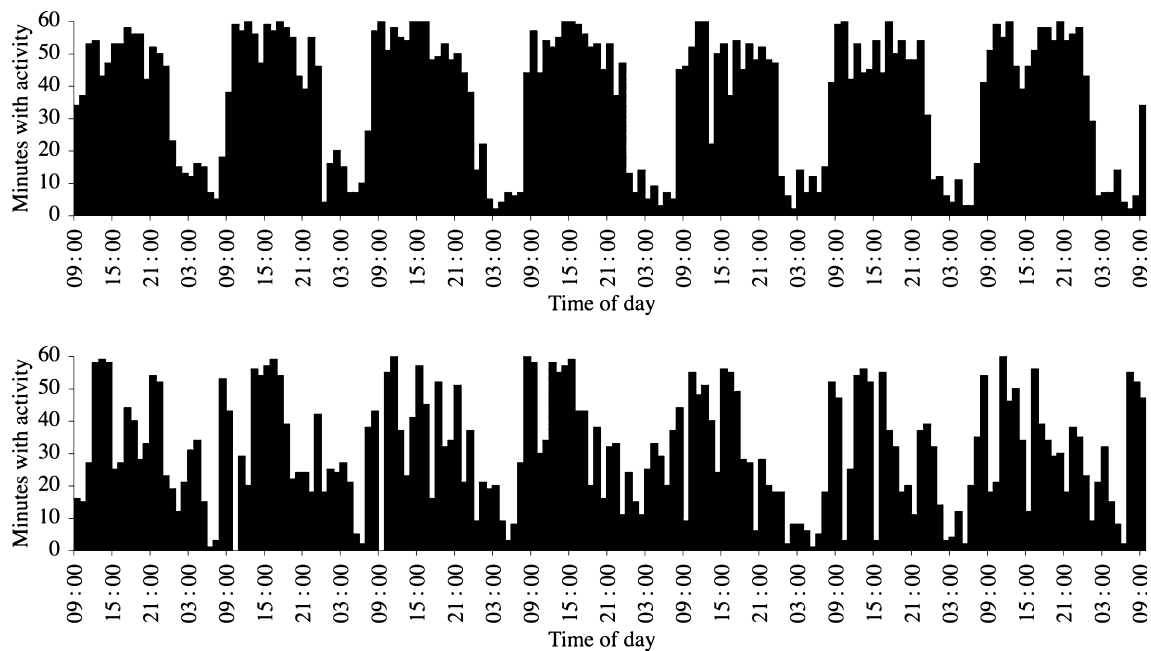


Figure 2. Circadian rest-activity rhythm in two participants. Upper panel displays the rest-activity rhythm of a participant with low IV who showed above average cognitive test performance. Lower panel represents the rest-activity rhythm of a participant with high IV who performed below average on the cognitive tests. IV: intradaily variability.

sleep onset. Furthermore, Jelacic *et al.* (2002) found a unique association between sleep complaints at baseline and cognition at follow-up, which persisted after controlling for cognition at baseline. This supports our first suggestion of fragmentation of the rest-activity rhythm as a predictor of cognitive function.

Another plausible explanation for this association focuses on underlying age-related changes in neural substrates. Aging is associated with a decline both in cognitive performance (e.g. Bopp and Verhaeghen, 2005; MacPherson *et al.*, 2002) and sleep-wake quality (e.g. Huang *et al.*, 2002). By affecting both cognition and the rest-activity rhythm, age-related changes in brain structures may account for the observed association between these variables. This may also explain why IV was the strongest predictor of all cognitive domains. Fragmentation of the rest-activity rhythm may be one of the most pronounced age-related changes; a previous study on actigraphic registration in aging demonstrated a strong effect of age on this variable (Huang *et al.*, 2002). As such, an index of the fragmentation of the rest-activity rhythm might be a very sensitive indicator of underlying age-related changes in brain structure and function. However, controlling for the effect of age only partly attenuated the results, and a significant association between cognition and fragmentation of the rhythm remained. This suggests a unique relationship between the rest-activity rhythm and cognitive functions that extends beyond a common underlying involvement of aging *per se*.

One possible limitation of the present study is that the majority of the subjects suffered from at least one cardiovascular risk factor. This limits extrapolation of the current observation to healthy community-dwelling elderly people, despite that the prevalence of cardiovascular risk factors might be quite high in this population (for example, prevalence of hypertension might be as high as 60–80%; Brindel *et al.*, 2006; Kanoni and Dedoussis, 2008). It is unclear, however, to what extent extrapolation is limited because the association between IV and cognition, despite diminished by controlling for confounders, remained significant. Similarly, the majority of the sample consisted of male participants. Although gender was included in the analysis as a potential confounder (and did not mediate the relationship between IV and cognition), generalization is limited. Finally, although history of a depression was one of the exclusion criteria of the present study, current depression was not considered but might well be important when one is examining factors in relation to the circadian rhythm (Roberts *et al.*, 2000). However, a previous study indicated a robust association between sleep and cognition regardless of depressive symptoms (Schmutte *et al.*, 2007).

Another potential limitation concerns the fact that no objective screening was performed to examine the possible presence of sleep disordered breathing (SDB). The prevalence of SDB might have been substantial in our study population, considering the existing overlap between cardiovascular risk factors, specifically cardiac disease such as congestive heart failure, and SDB (Benjamin and Lewis, 2008). The high

prevalence of these risk factors might indicate an increased prevalence of SDB in our study sample. As a risk factor for cognitive impairment (Spira *et al.*, 2008), SDB might actually mediate the association between cognition and IV in the current study. However, cardiovascular risk factors, and thereby the risk of SDB, were included as possible confounders in the analyses but did not mediate the relationship between IV and cognition. Furthermore, a reanalysis of the subsample of subjects without cardiac disease, which strongly diminishes the possibility of SDB to be present, still revealed significant correlations between IV and mental speed, memory, and executive function ($r = -0.292$, -0.291 , and -0.395 respectively). Although it is not very likely that SDB fully accounted for the relationship between IV and cognition in the present study, it is unknown to what extent SDB is related to the fragmentation of the rest-activity rhythm. This important topic should be addressed in future studies.

To conclude, a robust association between cognition and fragmentation of the rest-activity rhythm is present in elderly people. Further studies should focus on the possibility of causality and reversibility.

CONFLICTS OF INTERESTS

There are no conflicts of interest for any of the authors.

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